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EXAMINER	
MILNE, A	

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DATE MAILED: 12/07/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-30 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 1-30 are currently pending in U.S. Patent Application Number: 08/397,225.

The disclosure is objected to because of the following informalities: The specification should replace "promotor" with "promoter" in all places recited. Claim 23 should replace "glucocorticold" with "glucocorticoid". Page 25, line 37 "describe" should be changed to "described". Page 9, line 12, "supression" should be spelled "suppression". Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Applicants' claims recite the generation of adenoviruses that have had various regions of their genome deleted, including the E1, E2, E4, and late genes, more specifically, L1-L5. The adenoviruses constructed in the instant invention are also said to contain one or more heterologous DNA sequences. Applicants' claims also entail a cell line that has been infected by an adenovirus constructed and claimed in the instant application,

and that said cell line is necessary for the complementation of the defective recombinant adenovirus.

The specification fails to provide an enabling disclosure for the following reasons:

Applicants claims broadly encompass adenoviruses that have been constructed through the deletion of its late genes; however, applicants have not provided evidence for the construction of an adenovirus that has had any of its late genes, with the single exception of L5, removed. There is no guidance in the specification as to how deletion of all of the late genes, more specifically, L1-L4, could be accomplished, thereby requiring one of skill in the art to practice undue experimentation to construct an adenovirus as claimed with late gene deletions; and further that one of skill in the art could accomplish this task and still construct a functional adenovirus as is claimed in the instant application. Further, applicants have not enabled the construction of adenoviruses from all of the animal sources as broadly claimed, and there is no guidance on the differences that one may encounter in using adenoviruses from different species.

Regarding the claims to an adenovirus in which any of the genes E1-E4 and L1-L5 and any other "late genes" have been declared as "non-functional", the specification provides evidence only for the deletion of such regions, with the exception of L1-L4 and other "late genes". One of skill in the art would have to undertake undue experimentation to construct an adenovirus as

broadly claimed in which said genes are merely "non-functional", and further that the adenoviruses constructed would behave with a considerable amount of predictability.

Regarding claims to an adenovirus that contains a heterologous DNA sequence, the specification provides no guidance to the ordinary skilled worked on the construction of any adenoviruses containing any therapeutic genes, antisense genes, genes encoding antigenic peptides, or genes that permit the expression of heterologous genes inside the infected cell. The only working example present in the specification is that of lacZ gene insertion. However, one of skill in the art would be required to practice undue experimentation in practicing the invention as claimed because the breadth of the claims encompasses a large amount of genes(to be inserted into the adenoviral genome) d. ffering in origin, function, stability and size; with this in mind and considering the lack of guidance presented in the construction of the adenoviruses as broadly claimed, applicants have not enabled the present invention.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art

to practice the invention.

Claims 1-30 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that it is not clear what quantities of the indicated genes are encompassed by the phrase "at least one".

Claim 2 is vague and indefinite because it is not clear which origin will be the origin of the adenovirus.

Claim 3 is vague and indefinite because it is not clear what the term "group C" encompasses, (i.e. are these serotypes and if so which serotypes are specifically claimed in the instant application).

Claims 1, 7, and 8 are vague and indefinite because it is not clear which DNA sequences are encompassed by the term "a heterologous DNA sequence".

Claim 6 is vague and indefinite in that it is unclear what genes are encompassed by the term "late genes".

Claim 12 is vague and indefinite in that it is not clear what the quantitative metes and bounds of "one or more gene" are.

Claim 13 is confusing because it is not clear which

"therapeutic gene" applicants intend. The phrase "selected from the group of " should be considered.

Claim 14 is vague and indefinite because it is not clear if applicants are claiming "an antisense gene" or a "sequence whose expression in the target cell makes it possible to control the expression...".

Claim 15 and 16 are vague and indefinite because it is not clear as to which peptides are encompassed by the term "antigenic peptide". Further, claim 16 is indefinite because it is not clear as to which of the viruses or tumors listed are to be the target that the "antigenic peptide" is "specific for". Claim 16 is also vague because it is not clear what is encompassed by the term "tumors".

Claim 17 is vague and indefinite in that it is not clear what is intended by the phrase "sequences permitting the expression of .." and further what sequences are encompassed by this description, and further, what the metes and bounds of "one or more heterologous genes" are. There is no antecedent basis for the term "the infected cell".

Claim 18 is vague and indefinite because it is not clear what sequences are encompassed by the term "a signal sequence". Further, it is unclear what pathways are encompassed by the term "secretory pathways".

Claim 19 is vague and indefinite because it is not clear what functions are intended by the term "functions necessary for

the complementation". The claim is further vague in recitation of the term "infectible" because this does not clearly define what applicants intend, i.e. whether or not the cell line is "infectible" does not indicate that it will in fact be infected.

Claim 28 is vague and indefinite because it is not clear how many adenoviruses are encompassed by the term "at least one defective recombinant adenovirus".

Claim 30 is vague and indefinite because it is not clear what is encompassed by the term "a vehicle".

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Davis et al taken with Berkner and Bajocci et al and Weinberg et al and James.

Regarding the specific components involved in applicants'

adenoviral vectors,

Davis et al disclose a recombinant adenovirus containing a heterologous gene segment that codes for an antigen that is produced by a disease-causing organism. The genes can code for hepatitis B antigen, a rotavirus antigen, or an HIV antigen, column 3, lines 2 and 24, and the plasmids used in the viral constuction can contain SV40 signal sequences. The references states that the recombinant adenoviruses contain unaltered virion structural proteins, column 2, lines 54-56. Davis et al further state in column 10, lines 1-8 that: "In addition to the E1 and E3 regions, there are several other regions of the viral genome where the cassette containing promoter, tripartite leader, foreign gene and processing and polyadenylation signals may be inserted. These include a region between the E1a and E1b regions at the left and right ends of the genome, and at the E4 region, and between L5 and E4 regions." The reference further states that any type of adenovirus may be employed in the present invention, column 10, lines 40-45.

Berkner states on page 617, column 2, that deletion analysis of the ITR has shown that at least part of it is required for viral viability and that the ITR sequences alone are not sufficient for replication. It is further noted that plasmids containing the ITR's could theoretically be used to generate recombinants with very large inserts. Berkner states on page

617, column 1 that the ability to dispense with 2-3 Kb in E4 Ad sequences would be advantageous in vector development, and further that the E3 region of the viral genome is totally dispensable and can have DNA sequences inserted therein. Berkner further states on page 620, column 1, the use of a promoter, the MLP, in recombinant adenoviral vectors and that high viral titers achieved in the promoters presence, moreover, the major late promoter is very efficient. Berkner teaches on page 617 that the E2 region encodes a 72 K DNA binding protein. Therefore any vectors or cells containing this region would code for the 72 K protein. Berkner teaches on page 621, column 2 , the use of recombinant adenoviral vectors and that all that is required in cis are the ITR's and a packaging sequence.

Regarding cell lines, Berkner states on page 617, that W162 cell lines that express the E4 region have been created in attempts to determine E4 region role in DNA replication and other processes, (see column 1, lines 21-30). The reference teaches that 293 cells are used in which the E1 and E3 regions have already been deleted, and that potential deletions in the E4 region may permit even larger inserts. Furthermore, Berkner states that propagation of the virus in 293 cell lines makes scale-up for protein isolation practical and inexpensive. Berkner concludes the point in teaching on page 621, end of column 2, that the use of defective recombinants co-infected with wild type-Ad should be of value in generating transformed cell

lines.

Weinberg et al describe the propagation of W162 cells that were transfected with a restriction fragment containing E4 and that these cells permitted plaque formation by a E4 deleted adenoviral mutant. Weinberg further states on page 5383, column 2, that a cell line that would complement E4 mutants would be beneficial for isolation purposes.

Bajocchi et al disclose replication deficient recombinant adenovirus vectors that contain a therapeutic DNA sequence, more specifically the gene coding for α1-antitrypsin. The reference teaches the use of type 5 adenovirus that is classified in Group C, and that the use of this serotype is beneficial due to its lack of tumorigenicity, page 232, column 1.

James et al discloses the use of antisense genes in expression vectors including viral mediated systems, and that this type of gene transfer rarely results in genetic damage, and expression is directed at a high level. One of ordinary skill would have clear motivation to choose an adenoviral vector as a method of antisense gene transfer due to its many advantages as previously cited. More specifically, addressing the claim to a cell line that place E2 and E4 under the control of an inducible promoter and a cell line comprising the gene for the glucocorticoid receptor, Davis et al teach the use of a promoter but is not as specific in comparison to James who teaches on page

197, that without an appropriate promoter/enhancer and polyadenylation signal, an AR gene cannot produce antisense within a cell. The choice of the promoter is governed by the cell type involved, the level of expression required and whether it is desired that the antisense RNA should only be synthesized under particular circumstances, and that the promoter can include the glucocorticoid-inducible(implying a glucocorticoid requirement and receptor involvement within the cell)LTR from MMTV.

Therefore at the time that the invention was made, the early and late regions of adenovirus were known and that one of skill in the art would have had sufficient motivation to delete various portions of the genome in the interest of creating "room" in the viral genome for substantially large gene inserts. One of ordinary skill in the art would have had sufficient motivation to combine the adenoviruses as seen in Davis and further to modify them to be defective-recombinants" as taught by Berkner because the defective vectors have a clear advantage with large substitutions (>7.5Kb), and further to use adenoviruses in group C because they have a lower degree of tumorigenicity, and further to propagate the adenoviruses in cell lines that have the ability to complement adenoviruses that have certain genomic deletions as seen in Weinberg who states that it is possible to construct complementing cell lines for segments of viral DNA and further that this could be done for the adenoviral early regions, and

that propagation may occur in 293 cells, which as added by Brekner, makes propagation of the virus practical and less expensive. Therefore at the time that the invention was made, it was common knowledge in the art that recombinant viral vectors could be propagated in various cell lines and that discrimination between vector constructs and complementing cell lines could result in a cell line containing E1, E3, E4, late genes or signal sequences, since all of these had been identified in the adenovirus and that it was known that their removal could allow for insertion of large segments of DNA that could serve a therapeutic or antigenic purpose.

Regarding claims 28-30, the use of pharmaceutical compositions and vehicles of administration are effective variables routinely optimized by those of ordinary skill in the art and it would have been obvious to create a pharmaceutical composition containing applicants' disclosed recombinant adenoviral vectors since they are disclosed as being therapeutically effective.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be

reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne
10-13-95

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SUPERVISORY PATENT EXAMINER
GROUP 1800